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# Effect of post-discharge pharmacist-led follow-up on drug treatment in patients with deep venous thrombosis in primary hospitals in China

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**Abstract**: Warfarin and rivaroxaban were the two most commonly-used anticoagulant drugs for Deep venous thrombosis (DVT). The aim of this study was to explore the effects of post-discharge pharmacist-led follow-up on drug treatment in patients with DVT in primary hospitals from a pharmacological perspective. A total of 125 patients were recruited from July 2017 to June 2019 and randomized to either a control group or an intervention group. The control group was given routine medication guidance, clinical pharmacists followed up at 3 and 6 months after discharge. The intervention group was based on the control group and was followed up weekly for 6 months after discharge. For patients taking warfarin, the percentage of time in therapeutic range (TTR) and TTR ≥65% were significantly higher in the intervention group ($p<0.05$) and they also had less frequent dose changes. For patients taking warfarin or rivaroxaban, vascular ultrasonography showed better improvement rate in the intervention group ($p<0.05$). Pharmacist-led follow-up showed that the medication adherence ($p<0.05$) were significantly improved. There were lower risks of total and minor hemorrhage events and thrombosis events in the intervention group ($p<0.05$). Pharmacist-led follow-up not only reduced the risk of hemorrhage and thrombosis events, but also improved adherence to anticoagulation drugs.

**Keywords**: Deep venous thrombosis, follow-up, medication adherence, pharmacist, primary hospital.

## INTRODUCTION

Deep venous thrombosis (DVT) often occurs in the lower limbs, which was a venous reflux disorder caused by abnormal blood clotting in the deep veins. Collectively, DVT and pulmonary embolism (PE)were referred to as venous thromboembolism (VTE), which was the third most common vascular disease and had the third-highest fatality rate behind tumor and myocardial infarction (Alexander Brill,2021). The main adverse consequences of DVT were PE and post thrombotic syndrome (PTS), which can substantially decrease life quality of patients and can even be fatal (Lindner LH, 2021). Therefore, it had become the focus of international research (Zhang and Liu, 2017).

DVT patients need long-term anticoagulation and other treatments to prevent the spread or recurrence of thrombus (Yugo Yamashita, 2021). Commonly-used anticoagulant drugs included vitamin K inhibitor (such as warfarin), factor Xa inhibitor (rivaroxaban) and direct thrombin inhibitor (Vascular surgery group, 2017). The first two were studied before. Good medication adherence was a key factor in controlling spread and recurrence. Many patients had poor long-term medication adherence, especially those with a low education level and old age. And this reduced the efficacy of drug treatment or leaded to poor prognosis. Therefore, methods to improve patient medication adherence were urgently required.

The participation of clinical pharmacists can significantly improve medication adherence for chronic diseases, can reduce the incidence of adverse events, and can improve patient quality of life (Beate *et al*., 2014). However, there are less domestic implementation was low, especially in primary hospitals. Moreover, a few studies have reported whether the participation of clinical pharmacists can improve the medication adherence and safety of patients with DVT. Therefore, this study explored the effects of post-discharge pharmacist-led follow-up on medication adherence and adverse drug events in DVT patients in primary hospitals. The aim was to accumulate more practical experience for clinical pharmaceutical care and provide a reference for improving the effect of drug treatment.

## MATERIALS AND METHODS

### *Setting and subject recruitment*

We selected patients with DVT who were treated at a local hospital in De Zhou, China, from July 2017 to June 2019. Inclusion criteria were as follows: Patients diagnosed with DVT, who were discharged after treatment in the acute phase, patients treated with rivaroxaban or warfarin after discharge and participation in the study voluntary. The exclusion criteria were as follows: patients with psychiatric disorder, dysopia or dysaudia.

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The study was a double-blind randomised control trial with following-up for 6 months. Stratified area group randomization method was adopted and SAS 9.4 statistical software was used to generate random number grouping table. Patients were divided into two groups randomly: The control group and the intervention group.

The control group was given routine medication guidance, medication monitoring, health education and other pharmaceutical care by clinical pharmacists during hospitalization. Clinical pharmacists followed up by telephone at 3 and 6 months after discharge. The intervention group was based on the control group but was also followed up weekly for 6 months after discharge. All patients had a standardized form to monitor compliance each day, including the frequency, dose and duration of drugs taken, as well as, whether the patient missed a dose, took a wrong dose or overdose and hemorrhagic events or thrombosis. Hemorrhagic events included: hemorrhagic stroke, extracranial hemorrhage (bleeding of ≥300ml, hemoglobin decrease of >20g/L, or blood transfusion of >400ml). The patient was also asked to record any instances of minor hemorrhagic events such as: gingival bleeding, skin bleeding at one point or ecchymosis, conjunctival bleeding, microscopic hematuria, bloody sputum, gross hematuria, hemoptysis or hematemesis of <300ml, bloody or black feces and vaginal bleeding (Liu *et al*., 2017).

A pharmacy service file was established which included the patient's personal information and hospitalization record; and recorded the patient's medication status and advice given, drug replacement and dose adjustment, adverse reactions and treatment; and clinical prognosis after discharge. As the following up showed, the pharmacist repeated the key themes (such as drug, ADRs, laboratory monitoring, diet, adherence) and patient's report.

***Observation index***

The therapeutic effect of DVT was observed by vascular ultrasonography examination. Vascular ultrasonography showed it was effective in the disappearance or reduction of thrombus, while vascular ultrasonography showed no reduction of thrombus and the ineffective treatment. Patients taking warfarin were urged to review their International Normalized Ratio (INR) regularly to adjust warfarin dose, and given dietary recommendations to ensure a stable intake of foods rich in vitamin K. In the whole course of the study, the frequency of INR monitoring was driven by the pharmacists or patients, and the INR values were taken from the patient's laboratory test report. TTR was calculated by the Rosendaal method (Rosendaal *et al*., 1993), and all of the collected INR values were taken into account. And the target TTR was set to 65%.

We observed the times of taking medicine, missing medicine, self-reducing medicine frequency and reducing medicine quantity in the same period, and collect the data so as to reflect the patient's medication adherence.

At the end of follow-up, patient satisfaction was assessed by using a Patient Satisfaction Questionnaire based on PSQ-18 and the Chinese version (Hu *et al*., 2017). Seven scales were included: general satisfaction, pharmacist-patient communication and the following aspects of the follow-up: technical quality, interpersonal manner, financial aspects, timeliness, accessibility and convenience.

***Ethical approval***

This study was approved by a local hospital review board in De Zhou and by the research ethics committees. All the patients gave their written informed consent before inclusion.

## STATISTICAL ANALYSIS

Statistical data were analyzed using SPSS Statistics version 17.0. Measurement data were expressed as mean and standard deviation, which were compared by using a Student's t test. Counting data were compared by using Fisher's exact test. $P<0.05$ was considered statistically significant.

## RESULTS

***Patients***

From July 2017 to June 2019, there are totally 186 patients with DVT were diagnosed at a local hospital in De Zhou, China. Among them, 40 patients were excluded, while 146 patients were included and randomized in the study criteria: 73 patients were assigned into each group. Among the 146 patients, 21of them were excluded because of complications with other diseases and lack of cooperation. The remaining 125 patients including 62 males and 63 females, aged from 31 to 87 years old (mean 62.8). These patients were then placed into the intervention groups (n=61) and control (n=64) groups (Fig. 1). The intervention group included 33 (50.8%) male patients with the median age 63.8: 40 patients received warfarin and 21 received rivaroxaban. The control group included 29 (45.3%) male patients with the median age 61.8: 49 patients received warfarin and 15 received rivaroxaban. There were no statistically significant differences in gender, age, education and the proportion of patients taking warfarin or rivaroxaban between the two groups ($p>0.05$), which indicated that the data were comparable. The patient demographics of this study were provided in table 1.

**Table 1**: Patient demographics.

| Patient demographics | Intervention group (n = 61) | Control group (n = 64) | *P* |
|---|---|---|---|
| Age | 63.80 ± 12.09 | 61.89 ± 11.52 | 0.371 |
| Sex (male: female) | 1.18:1 | 0.83:1 | 0.326 |
| Proportion of administration of Warfarin: rivaroxaban | 1.90:1 | 3.06:1 | 0.313 |
| Education: | | | 0.884 |
| No formal education | 19 (31.1%) | 21 (32.8%) | |
| Elementary school | 30 (49.2%) | 28 (43.8%) | |
| High school | 9 (14.8%) | 10 (15.6%) | |
| College | 3 (4.9%) | 5 (7.8%) | |

Values indicate the results of statistical test.

**Table 2**: Related indicators in patients taking warfarin.

| Related indicators in patients taking warfarin | Intervention group (n = 40) | Control group (n = 49) | *P* |
|---|---|---|---|
| Percentage of time in therapeutic range (TTR, %) | 73.22 ± 11.32 | 60.15 ± 14.75 | 0.014 |
| TTR ≥ 65% | 31 (77.5%) | 22 (44.9%) | 0.002 |
| Frequency of dose change | | | 0.009 |
| 0 | 11 (27.5%) | 5 (10.2%) | |
| 1 | 20 (50.0%) | 16 (32.7%) | |
| 2 | 6 (15.0%) | 19 (38.8%) | |
| ≥3 | 3 (27.5%) | 9 (18.4%) | |
| Vascular ultrasound indicated improvement | 31 (77.5%) | 23 (46.9%) | 0.003 |
| Medication adherence | | | 0.004 |
| Number of cases in the same time range: | 28 (70.0%) | 19 (38.8%) | 0.003 |
| Self-reduction of medication frequency | 4 (10.0%) | 6 (12.2%) | 0.505 |
| Missed doses | 5 (12.5%) | 19 (38.8%) | 0.005 |
| Low doses | 3 (7.5%) | 5 (10.2%) | 0.476 |
| Steady intake of vitamin K | 33 (82.5%) | 24 (49.0%) | 0.001 |

Values indicate the results of statistical test.

**Table 3**: Related indicators in patients taking rivaroxaban

| Related indicators in patients taking rivaroxaban | Intervention group (n = 21) | Control group (n = 15) | *p* |
|---|---|---|---|
| Vascular ultrasound indicated improvement | 19 (90.5%) | 8 (53.3%) | 0.019 |
| Medication adherence | | | 0.024 |
| Number of cases in the same time period | 16 (76.2%) | 5 (33.3%) | 0.013 |
| Self-reduction of medication frequency | 1 (4.8%) | 5 (33.3%) | 0.035 |
| Missed doses | 3 (14.2%) | 3 (20.0%) | 0.493 |
| Low doses | 1 (4.8%) | 2 (13.4%) | 0.373 |

Values indicate the results of statistical test.

**Table 4**: Adverse events

| Adverse events | Intervention group (n = 61) | Control group (n = 64) | *p* |
|---|---|---|---|
| Hemorrhagic stroke | 1 (1.64%) | 8 (12.5%) | 0.019 |
| Minor hemorrhage events | 7 (11.8%) | 20 (31.3%) | 0.007 |
| Thrombosis events | 0 | 5 (7.8%) | 0.033 |

Values indicate the results of statistical test.

**Table 5**: Patient satisfaction

| Patient satisfaction | Intervention group (n = 61) | Control group (n = 64) | *p* |
|---|---|---|---|
| General satisfaction | 4.1 ± 0.81 | 3.6 ± 0.91 | 0.041 |
| Follow-up technical quality | 4.1 ± 0.68 | 3.9 ± 0.72 | 0.282 |
| Follow-up interpersonal manner | 4.1 ± 0.74 | 3.6 ± 0.69 | 0.019 |
| Pharmacist patient communication | 4.2 ± 0.72 | 3.5 ± 0.73 | 0.003 |
| Follow-up financial aspects | 3.9 ± 0.73 | 3.6 ± 0.94 | 0.391 |
| Follow-up timeliness | 4.1 ± 0.85 | 3.5 ± 1.02 | 0.048 |
| Follow-up accessibility and convenience | 4.3 ± 0.67 | 3.7 ± 1.01 | 0.017 |

Values indicate the results of statistical test.

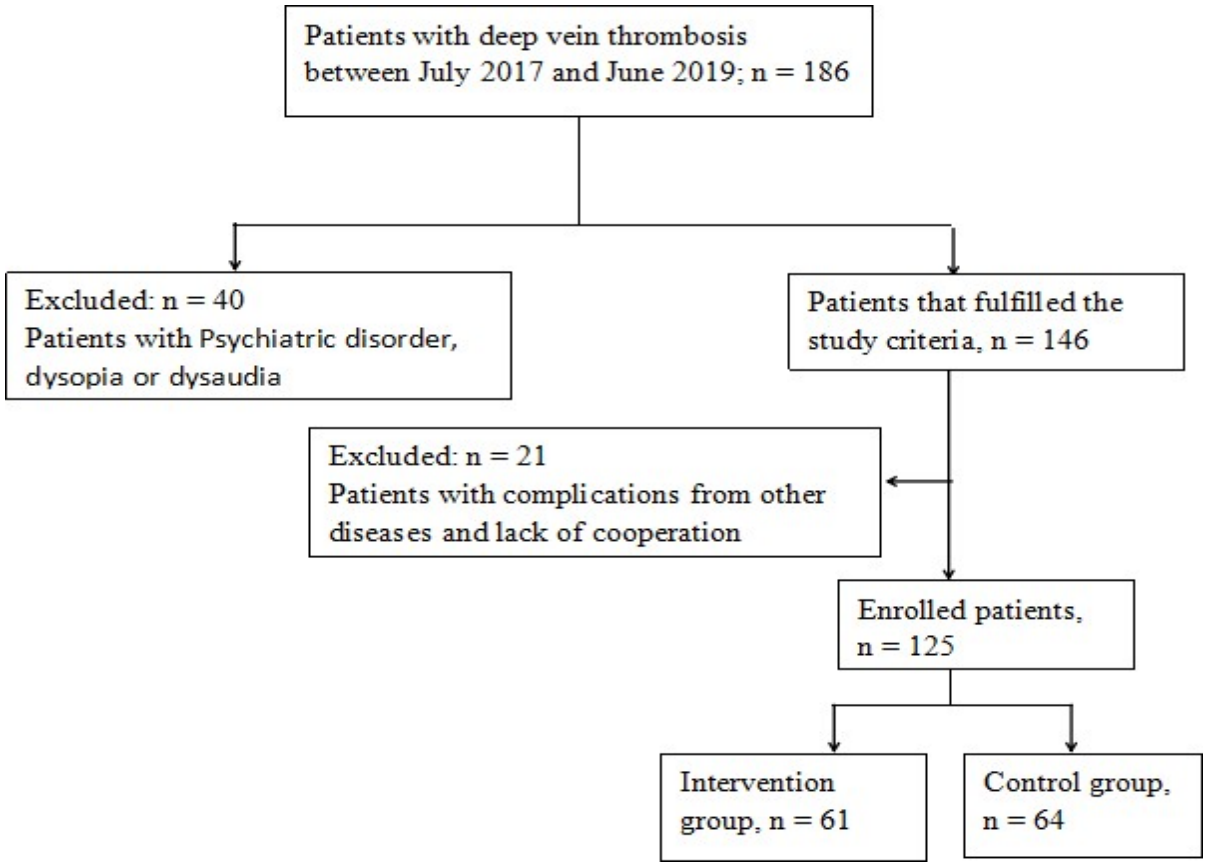


**Fig. 1**: Flowchart showing the process of patient selection.

***Therapeutic effect index outcomes***

The TTR and the proportion of patients with a TTR≥65% in the intervention group (73.22% ± 11.32; 77.5%) were higher than in the control group (60.15% ± 14.75; 44.9%; P<0.05). Dose changes in the intervention group were also made less frequently than in the control group (p<0.05). It was found on vascular ultrasonography, the improvement rate was higher in the intervention group than in the control group in patients taking warfarin or rivaroxaban (p<0.05). Warfarin-related outcomes for the two groups were shown in table 2 and the rivaroxaban-related outcomes were shown in table 3.

***Medication adherence***

Medication adherence included four main aspects: number of cases taking medication in the same period, self-reduction of medication frequency, and rate of missed and low doses. Patients taking warfarin had significantly better medication adherence in the intervention group than in the control group (p<0.05). The number of cases in the same period was also higher in intervention group (70.0%) than in control group (38.8%; p<0.05). The rate of missed doses was significantly lower in intervention group (12.5%) than in control group (38.8%; p<0.05). Neither the self-reduction of medication frequency

(10.0%, 12.2%; p>0.05) nor the the rate of low doses (7.5%,10.2%; p>0.05) did not differ between the intervention and control groups. The number of stable intake cases of vitamin K in the intervention group (82.5%) was significantly higher than in the control group (49.0%; p<0.01; table 2).

Patients taking rivaroxaban also had better medication adherence in the intervention group than in the control group (p<0.05). The number of cases in the same period was larger in the intervention group (76.2%) than in the control group (33.3%; p<0.05). The self-reduction of medication frequency was smaller in the intervention group (4.8%) than in the control group (33.3%; p<0.05). The rate of missed doses (14.2% vs 20%) and low doses (4.8% vs13.4%) were not different between the two groups (p>0.05; table 3).

***Adverse events***

The adverse events seen were mainly hemorrhage and thrombosis. The incidence of hemorrhagic stroke was smaller in the intervention group (1.64%) than in the control group (12.5%; p<0.05) and all incidences occurred in patients taking warfarin. There were 7 non-massive bleeding events in the intervention group, including 6 patients taking warfarin (of which 5 had skin bleeding, and 1 had black feces) and 1 patient taking rivaroxaban (black feces). The incidence of these events was significantly smaller in the intervention group (11.8%) than in the control group (31.3%; p<0.01), including 18 patients on warfarin (of which 12 showed skin bleeding, 3 black feces, and 3 vaginal bleeding) and 2 patients taking rivaroxaban (1 skin bleeding, 1 black feces). The incidence of thrombosis events in the intervention group (0) was also significantly smaller than in the control group (7.8%; p<0.05, table 4), including 4 patients on warfarin and 1 on rivaroxaban.

***Patient satisfaction***

The results of the patient satisfaction survey were shown in table 5. The scores in the intervention group were higher (p<0.05) than the control group across all areas except follow-up technical quality and financial aspects, which were not different (p>0.05).

## DISCUSSION

In recent years, the prevalence of DVT in hospitalized patients has increased. (R. J. Dirschinger *et al*., 2021). Warfarin has been available for over 60 years, which was used to prevent systemic embolism in patients with atrial fibrillation or artificial heart valves, as well as acute DVT or PE (Paul P *et al*., 2013). However, due to its narrow therapeutic index, frequent drug-food interactions, and unpredictable dose responses, achieving effective and safe treatment remains a challenge (Slaven *et al*., 2018). As many factors influenced the anticoagulation of warfarin, frequent monitoring of the international normalized ratio (INR) was required to maximize its efficacy and safety (Ansell *et al*., 2008). Moderate intensity (INR 2.0-3.0) anticoagulant therapy was the current clinical standard (Vascular surgery group, 2017). The frequency of INR monitoring was adjusted according to whether the patient was stable in the target range and the quality of anticoagulation was expressed as TTR (Slaven *et al*., 2018). A TTR of ≥65% indicated maximum benefit, which can prevent thrombosis effectively and minimize the occurrence of adverse events such as bleeding (Jones *et al*., 2014).

We found that both TTR and TTR ≥65% were significantly increased in the intervention group, indicating that the intervention patients spent more time in the therapeutic range compared to the controls. This was consistent with Falamić *et al* (Slaven *et al*.,2018). Previous non-randomized studies on the impact of pharmacists' interventions in rural patients for warfarin treatment showed that pharmacists play a crucial part in achieving safe and effective warfarin treatment (Harrison *et al*., 2015). We also compared other measures of efficacy in patients taking warfarin, such as frequency of dose change and vascular ultrasound-indicated improvement. We found that the frequency of dose change was smaller in the intervention group and dosage was stabilized in a suitable range. In addition, vascular ultrasonography showed better improvement in the intervention group. Similar results have previously been reported (Gupta *et al*., 2015).

Rivaroxaban, a new type of anticoagulant, had high bio-availability and was safe and easy to use, had no drug cross-resistance, required no monitoring to adjust the dose (Zhao *et al*., 2016) and there were no effects of diet (Quan *et al*., 2018). In our study, vascular ultrasonography showed better improvement in the intervention group. The lower rate in the control group may be related to the relatively high price, making patient adherence more difficult. These findings were consistent with a study by Jianshuang *et al* (Cui *et al*., 2019).

Since the pharmacokinetics of warfarin are influenced by a variety of drugs, food, physiological and pathological states, as well as genetic factors, individual differences vary widely. Therefore the effective control of anticoagulation efficacy was inseparable from patient cooperation. Pharmacists were trained for dosing adjustment, drug-drug or drug-food interaction identification and adverse drug event monitoring. Previous studies have also shown that clinical pharmacists can reduce the incidence of complications and improve patient compliance with anticoagulation therapy through guidance and education after surgery (Zhou and Bao, 2015).

For patients taking warfarin, the pharmacist explained the precautions for medication, the importance of following the doctor's advice, and the risk of self-adjusting the dose. The results showed that the number of cases in the same period was significantly increased and missed doses were significantly reduced, but the proportion of patients with self-reduction of medication frequency and low doses did not significantly decrease. This may have been related to the low level of patient education and insufficient attention paid to warfarin medication. The pharmacist also explained to patients that the mechanism of warfarin action is by interfering with vitamin K-dependent coagulation factors. Therefore food rich in vitamin K (such as liver, green vegetables including spinach, lettuce and asparagus) can weaken the anticoagulant effect of warfarin. In contrast, foods such as garlic, ginger, papaya, grapefruit juice and mango can enhance the anticoagulant effect of warfarin. As vitamin K intake was a predictor of TTR and an important factor affecting anticoagulant quality. Therefore, patients need to maintain a relatively constant intake of vitamin K to ensure a stable anticoagulant effect. We found the interventions have a better adherence and stable vitamin K intake, demonstrating the wide range of benefits of pharmacist intervention. This was consistent with a previous study which found that a pharmacist-led telephone intervention can significantly improve medication adherence (Imogen *et al*.,2016).

Our study also found that ,for patients taking rivaroxaban, the number of cases in the same period was significantly increased and the proportion of patients with self-reduction of medication frequency was significantly reduced, while the proportion of missed and low doses did not decrease significantly compared to the control group. This may be due to the relatively high price of rivaroxaban, the mental health of some patients, the low level of education and the lack of awareness of the importance of medication adherence. In general, pharmacist follow-up can significantly increase medication adherence, which was consistent with a study by Xiang *et al* (Xiong *et al*., 2019).

Drugs have two sides. While playing a therapeutic role, they may also cause adverse drug reactions, which may lead to hospitalization or prolonged hospitalization, or even death (Hoonhout *et al*., 2010). The occurrence of anticoagulation-related complications in patients taking warfarin was associated with many factors. Pharmacists guided patients and their families to self-monitor and rapidly adjust the dose of drugs in response. Our research demonstrated a lower risk of total and minor hemorrhage events and thrombosis events in the intervention group. This may be related to better medication adherence, regular medication and stable intake of vitamin K. Individuals who were treated with rivaroxaban suffered gastrointestinal bleeding, which may be associated with the higher incidence of hemorrhage in elderly patients (Hou, 2019). Similar results were obtained in two previous studies (Burgazli *et al*., 2013). One previous study showed that medication review with follow-up was a cost effective intervention (Jodar *et al*., 2015). Our research showed that general satisfaction, pharmacist-patient communication, and follow-up interpersonal manner, timeliness, accessibility and convenience were all significantly higher in the intervention group. This indicated that pharmacists' professional knowledge was recognized by patients and improved the quality of follow-up.

***Limitations***

In this study, patients' data were collected through the pharmacist-led telephone follow-up and cases in the hospital. Although many factors that might have influenced the results of the study were excluded, the completeness and accuracy of the data were affected by the skill of the assessors. Compared with large-scale international clinical trials, our study had a small sample size and limited observation indicators. The reliability of the conclusion needs to be confirmed with further scientific, rigorous and large-scale experiments.

## CONCLUSIONS

In the present study, we tested the effect of pharmacist-led follow-up on medication adherence in DVT patients in mainland China. Our study demonstrated that this intervention not only decreased the risk of hemorrhage and thrombosis events, but also improved the safety and effectiveness of anticoagulation drugs and improved adherence to medication. Pharmacist-led follow-up showed benefits for warfarin or rivaroxaban anticoagulation therapy in primary hospitals. This intervention may be accepted as a proven pharmaceutical anticoagulation model in China which could be popularized and promoted worldwide.

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